Sexing the X: How the X Became the "Female Chromosome"

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Unexpected." "Counterintuitive." "Intellectually surprising."[1] These were among the exclamations of researchers upon the 2001 discovery that the human X chromosome carries a large collection of male sperm genes (Wang et al. 2001). Although both males and females possess an X chromosome, the X is frequently typed as the "female chromosome" and researchers assume it carries the genes for femaleness. This essay traces the origins of this long-standing and infrequently questioned association of the X with femaleness and examines the influence of this assumption on historical and contemporary genetic theories of sex and gender difference.

Humans possess twenty-two pairs of autosomal chromosomes and one pair of sex chromosomes—X and Y for males, X and X for females. Today it is well established that the Y carries a critical genetic switch for male sex determination. The X, however, has no parallel relationship to femaleness. Female sexual development is directed by hormones acting in concert with genes carried by many chromosomes and is not localized to the X. Indeed, the X is arguably more important to male biology, given the large number of X-linked diseases to which men are uniquely exposed. Despite this, researchers attribute feminine behavior to the X itself and assume that female genes and traits are located on it. Researchers look to the X to explain sex differences and female quirks and weaknesses and have argued that men are superior because they possess one fewer X than females.

The X chromosome offers a poignant example of how the gendering of objects of biological study can shape scientific knowledge. Moving freely

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[1] Seema Kuman, "Genes for Early Sperm Production Found to Reside on X Chromosome," Massachusetts Institute of Technology press release, April 4, 2001. http://web.mit.edu/newsoffice/2001/sperm-0404.

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between stereotypical conceptions of femininity and models of the X chromosome, X-chromosomal theories of sex differences reveal a circular form of reasoning that is familiar in gender analysis of biology. As Evelyn Fox Keller writes: "A basic form common to many [feminist analyses of science] revolves around the identification of synecdochic (or part for whole) errors of the following sort: (a) the world of human bodies is divided into two kinds, male and female (i.e., by sex); (b) additional (extraphysical) properties are culturally attributed to these bodies (e.g., active/passive, independent/dependent, primary/secondary: read *gender*); and (c) the same properties that have been ascribed to the whole are then attributed to the subcategories of, or processes associated with, these bodies" (1995, 87). A classic historical example of this phenomenon is the gendering of the egg and sperm in mid-twentieth-century medical textbooks, documented by Emily Martin (1991). A second example is the gendering of the sex steroids estrogen and testosterone, as told by Nelly Oudshoorn (1994) and Anne Fausto-Sterling (2000).

Rooted in history and philosophy of science, and drawing on the interdisciplinary methods and questions of feminist science studies forged by scholars such as Fausto-Sterling, Keller, Donna Haraway, and Martin, this essay investigates the sexing of the X in a variety of scientific materials both internal and external to the biosciences. The sexing of the X, I argue, represents a case of gender-ideological bias in science, both historically and in the present day. More generally, it demonstrates how biological objects and concepts may take on a gendered valence as they circulate between popular and scientific realms.

The female X has its roots in early sex chromosome science, which assumed for half a century—until the 1950s, when the Y was confirmed as the carrier of the sex-determining locus—that the X was female determining in humans. In the first part of what follows, I document the contingent technical, material, and ideological factors that led to the feminization of the X during the first decades of sex chromosome research and track the introduction of the "female chromosome" into human genetics at midcentury. In the second part, I demonstrate the continuing influence of the historical feminization of the X on genetic research, exemplified by "X chromosome mosaicism" theories of female biology, behavior, and disease. Focusing on the case of X-mosaicism theories of the higher incidence of autoimmunity in women, I show how the assumption that the X is the female chromosome operates to sustain and cohere hypotheses of dubious empirical merit in research areas urgently relevant to women's health.

The feminine chromosome

Scientific and popular literature on the sex chromosomes is rich with examples of the gendering of the X and Y. The X is dubbed the "female chromosome," takes the feminine pronoun "she," and has been described as the "big sister" to "her derelict brother that is the Y" (Vallender, Pearson, and Lahn 2005, 343) and as the "sexy" chromosome (Graves, Gecz, and Hameister 2002). The X is frequently associated with the mysteriousness and variability of the feminine, as in a 2005 *Science* article headlined "She Moves in Mysterious Ways" and beginning, "The human X chromosome is a study in contradictions" (Gunter 2005, 279). The X is also described in traditionally gendered terms as the more sociable, controlling, conservative, monotonous, and motherly of the two sex chromosomes. Similarly, the Y is a "he" and ascribed traditional masculine qualities—macho, active, clever, wily, dominant, as well as degenerate, lazy, and hyperactive.[2]

There are three common gendered tropes in popular and scientific writing on the sex chromosomes. The first is the portrayal of the X and Y as a heterosexual couple with traditionally gendered opposite or complementary roles and behaviors. For instance, MIT geneticist David Page says, "The Y married up, the X married down. . . . The Y wants to maintain himself but doesn't know how. . . . He's falling apart, like the guy who can't manage to get a doctor's appointment or can't clean up the house or apartment unless his wife does it" (Dowd 2005). Biologist and science writer David Bainbridge (2003) describes the evolutionary history of the X and Y as a "sad divorce" (56) set in motion when the "couple first stopped dancing," after which "they almost stopped communicating completely" (58). The X is now an "estranged partner" of the Y, he writes, "having to resort to complex tricks" (145). Oxford University geneticist Brian Sykes (2003) similarly describes the X and Y as having a "once happy marriage" (283–84) full of "intimate exchanges" (42–43) now reduced to only an occasional "kiss on the cheek" (44). A 2006 article on X-X pairing in females in *Science* by Pennsylvania State University geneticist Laura Carrel is headlined "'X'-Rated Chromosomal Rendezvous" (2006).

Second, sex chromosome biology is often conceptualized as a war of the sexes. In Matt Ridley's *Genome: The Autobiography of a Species in 23 Chapters* (1999), the chapter on the X and Y chromosomes is titled "Con-

[2] See, e.g., Burgoyne (1998), Angier (1999, 2007), Graves (2000), and Bainbridge (2003).

flict" and relates a story, straight from *Men Are from Mars, Women Are from Venus* (Gray 1992), of two chromosomes locked in antagonism and never able to understand each other (Ridley 1999, 107). A 2007 *ScienceNOW Daily News* article similarly insists on describing a finding about the Z chromosome in male birds (the equivalent of the X in humans) as demonstrating "A Genetic Battle of the Sexes" (Pain 2007), while Bainbridge (2003) describes the lack of a second X in males as a "divisive . . . discrepancy between boys and girls" (83), a genetic basis for the supposed war of the sexes.

Third, sex chromosome researchers promote the X and Y as symbols of maleness and femaleness with which individuals are expected to identify and in which they might take pride. Sykes offers the Y chromosome as a totem of male bonding, urges males to celebrate their unique Y chromosomes, and calls for them to join together to save the Y from extinction in his 2003 *Adam's Curse: A Future without Men*. Females are also encouraged to identify with their Xs. Natalie Angier (1999) urges that women "must take pride in our X chromosomes. . . . They define femaleness" (26). The "XX Factor" is a widely syndicated column about women's work/life issues on Slate.com, with the slogan "What Women Really Think"; it is also the name of an annual competition for female video gamers.[3] The promotional video for the Society for Women's Health Research, designed to convince the viewer of how very different men and women really are, is titled "What a Difference an X Makes!" (Society for Women's Health Research 2008).

How the X became the female chromosome

The notion of the X as the female chromosome arises from its history as an object of research and its ensuing gendered valence within biological and popular theories of sex. It was originally assumed that the X, not the Y, was the sex-determining chromosome in humans. Theophilus S. Painter, the American cytogeneticist who in 1924 first described the human sex chromosomes, dubbed XX "the female chromosome complex" (1924, 509), the X the "female-producing chromosome" (509), and males as "heterozygous for sex" (522), as they possess only one X. This founding idea, that the X is "female-producing" (509) or female tending, focused theories of the biological determination of femaleness exclusively on the X well into the twentieth century.

[3] See *Slate*'s "The XX Factor: What Women Really Think" blog at http://www.slate.com/blogs/xx_factor.html.

Historically contingent technical and material factors also helped to brand the X as female. The dominance of studies of the fruit fly *Drosophila* in the first half-century of genetic research played a central role. Unlike in mammals, in *Drosophila* the X is female determining. This is a threshold effect, in which sex is determined by the ratio of autosomes to X chromosomes, with more Xs producing femaleness. In textbook explanations of sex chromosomes from the first quarter of the century, an ink drawing of *Drosophila* chromosomes was ubiquitously used to illustrate the section on the chromosomal theory of sex (Morgan 1915, 7; Wilson 1925). So pervasive were *Drosophila*'s X and Y as the model for the sex chromosomes that the leading American geneticist, Thomas H. Morgan, dubbed the XX/XY chromosome constitution the "Drosophila type," writing that "The genetic evidence so far gained has placed in the Drosophila type the following animal forms: Drosophila, man, cat; and the plants, *Lychnis* and *Bryonia*" (1915, 78–79). The *Drosophila* model suggested that in humans, as in flies, the X should be expected to determine femaleness.

In the early days chromosomes were also studied almost exclusively in male gametes—the sperm. Looking at sperm, which as reproductive cells possess only one member of each chromosome set, a perfect dichotomy appeared: half the sperm cells had the X, and half did not. This led to a hyperbinary view of the X and Y. The sperm with an X always produces a female, and the X in the males' sperm is always inherited from the female parent. Failing to distinguish between the "sex" of the gamete and the sex of the organism, this distorted perspective helped to prematurely assign the X to femaleness.

Cytologists were originally "spermatologists" (Voeller 1968, 78–80), and spermatology played a large role in setting the research agenda, context, and motivation for sex chromosome studies. Sperm are plentiful, accessible, and easier to study than eggs or other human tissue. Thus, there are good reasons that male gametes were early chromosome researchers' tissue of choice. Nonetheless, the focus on sperm introduced a bias into early sex chromosome research. The centrality of maleness and male tissue to this research led scientists to the conclusion that the X is female and the Y is male. Had researchers looked at somatic tissue, the dichotomy would have been far less clear-cut: both males and females possess at least one X.

The human cytogenetic research revolution of the late 1950s and 1960s, which revealed that it is the Y that determines sex, marked the demise of the X-chromosomal model of human femaleness. After World War II, human genetics research reemerged in the wake of massive US investments in education, life science research, and medicine. Charged

with the task of assessing the long-term health and biological consequences of nuclear fallout, human cytogenetics—the study of the structure, behavior, and function of human chromosomes—burst onto the scene in the 1950s with a series of profound and triumphant discoveries. These included confirmation that humans possess forty-six chromosomes (rather than forty-eight, as had been universally believed); the revelation that an extra chromosome 21 causes Down syndrome; the understanding that the Y, not the X, is sex determining; and the identification, through population screening, of a host of surprisingly common human sex chromosome anomalies (see de Chadarevian 2006; Harper 2006).

The first significant breakthrough for human sex chromosome research was the identification of a condensed body present only in female cells. Discovered in 1949, the Barr body, an artifact of the presence of two X chromosomes, suddenly allowed nuclear sexing of any human cell (Barr and Bertram 1949). Murray Barr described the revelation that the "nuclei bear a clear imprint of sex" (Barr 1959, 681) as the "principle of nuclear sexual dimorphism" (682). The notion that every cell has a sex shifted the terms of human sex research and ushered sex difference into the genetic age. Screening for the presence of a Barr body allowed sex chromosome aneuploidies (numerical errors), such as Turner syndrome (XO) and Klinefelter syndrome (XXY), as well as a host of exotics, such as XXXs, XXXYs, XYYs, to be detected well before more detailed chromosome analysis and visualization techniques became available.

By the 1960s, human sex chromosome aneuploidies and other chromosomal anomalies had become potent symbols of the fascinating and exciting new genetics. The historian of midcentury genetics Soraya de Chadarevian (2006, 724–25) argues that this chromosome symbolism, along with the representational schema of the human karyotype, was the public icon of modern genetics in the 1950s and 1960s, before the double helix took its place. It was through this imagery, and the novelty of sex chromosome aneuploidies, that the public first became widely conscious of the X and Y as the molecular pillars of biological femaleness and maleness.

The official findings of human cytogenetics of the 1950s and 1960s were as follows: Human males and females possess twenty-two pairs of autosomes and a pair of sex chromosomes. Males have an X and a Y, and females have two X chromosomes. In females one X in each cell is inactivated early in development, equalizing dosage of X-chromosomal genes in males and females. Subsequent research revealed that the Y chromosome primarily carries a gene that initiates male sexual development and bears few other genes. In contrast, the X chromosome is similar to

an autosome, with more than a thousand genes. The X plays no special role in female development, which is controlled by a variety of genes on several different chromosomes.

The idea that the X was female determining was promptly discarded in light of these new findings. The female or feminine resonance that had accumulated around the X chromosome, however, did not fall away. As Fiona Alice Miller (2003) notes with respect to the term "Mongolism" for trisomy 21 (Down syndrome), "Contrary to conventional beliefs about new, breakthrough technologies, the introduction of chromosome analysis in the late 1960s did not displace existing standards of interpretation and practice" (76). Old habits and the force of the idea of a molecular gender binary revealed in the X and Y were irresistible. As the Y would be the male chromosome, the X would continue to be the female one.

Researchers did not give up the search for a relationship between the double X and femaleness in the wake of the 1959 finding that the Y is sex determining. They would continue to ask: What does the extra X do for females? What does an exposed, single X do for males? Elaborated in human genetics over the coming decades, the X and Y became sites for the enactment and rediscovery of traditional gender roles and stereotypes.

X-chromosomal theories of human sex differences

The question of whether the second X bestows human females with something extra, or whether it is more advantageous to have a single X chromosome, a question charged with gender politics, stalked the X from its earliest appearance in the public and scientific consciousness. Though human chromosome research was sporadic prior to the 1950s, the notion that human females carry an extra chromosome found its way into the scientific and social discourse around gender, a discourse that seems to have widely accepted the idea that the facts of biology would help to settle the sex wars and that we should expect to find definitive proof in the X of a sexual hierarchy.

On one side was the idea that double-X females are superior, advantaged, or special as a result of their extra X. This was appropriated by women's advocates: "The ancient idea that the female is essentially an undeveloped male seems to be finally disproved by the fact that it requires more determiners—usually one more chromosome, or a larger sex chromosome—to produce a female than a male," pronounced the feminist psychologist Helen Thompson Woolley (1914, 354). Even the notorious antifeminist Louis Berman conceded in his 1921 *The Glands Regulating Personality* that biologists could no longer seek the source of female in-

feriority in the chromosomes: "For the time being, let the feminists glory in the fact that they have two more chromosomes to each cell than their opponents. Certainly there can be no talk here of a natural inferiority of women" (1921, 136).[4] The anthropologist and public intellectual Ashley Montagu marshaled the notion of female X chromosome advantage in his 1953 text *The Natural Superiority of Women*. In a chapter titled "'X' Doesn't Equal 'Y,'" Montagu argued that it is "to the presence of two well appointed, well furnished X-chromosomes that the female owes her biological superiority" (1953, 76). Males, with their "X-chromosomal deficiency" (76), fall prey to such diseases as hemophilia and colorblindness, and countless other speculated weaknesses, while females, owing to an extra X, are "constitutionally stronger than the male" (81). Montagu asserted that females' extra X "lies at the base of practically all the differences between the sexes and the biological superiority of the female to the male" (74).

The discourse of female X-chromosomal superiority persisted in the second half of the twentieth century and even continues today. The size of the X and its large number of genes is frequently celebrated, and great emphasis is placed on the notion that, due to the second X, females have more genetic material than males. For example, *Time* magazine reported in 1963: "Because the X chromosome is so much bigger than the Y, women with two X's have 4 percent more genetic material—the vital deoxyribonucleic acid, or DNA—than men. Geneticists have speculated that this might explain women's longer life span. . . . [This] definitely gives women an inherent advantage over men" ("Research Makes It Official," 1963). Johns Hopkins geneticist Barbara R. Migeon argues that the second X means that "females have a little extra determinant" compared with males, which "bestows a remarkable biological advantage" (2007, 208). "When it comes to the battle of the sexes," writes E. J. Mundell (2007), reporting on Migeon's work, "nature hands women extra ammunition right from the start. The reason, according to geneticists: Females are gifted with two copies of the powerful X chromosome, while males are born with only one X, plus the relatively weak Y chromosome." Migeon, whose research I will return to below, even argues that the extra genetic material might account for why females and males have a different sense of humor and could explain why "from the first

[4] Berman's assertion that females possess "two more chromosomes" reflects the understanding of female-determining gametes as carrying an "extra" X chromosome. If females receive an extra chromosome from each parent, then in the full chromosome complement, females would be expected to have two more chromosomes than males.

days of school, girls outperform boys, are more attentive, and are more persistent at tasks" (2006, 1432–33).[5]

Countering claims of female X-chromosome superiority has been the far more influential notion that females are the weaker sex precisely because they carry an extra X chromosome. In the early twentieth century, prominent scientists asserted that the single X provided the biological mechanism for superior male cognition. They argued that while the single X may subject males to damaged genes on the X, it also exposes them more wholly to advantageous genes. The risks that males take with their sole X are countered by rich potential rewards. While females enjoy the security of a second X, it dulls their potential for extraordinariness. Males are superior where it counts: intelligence.

Highly influential in sex difference research, the "greater male variability" theory of male intellectual superiority framed research on cognitive differences between males and females from the 1870s to the 1930s. It was subsequently discredited with the rise of new experimental techniques, greater statistical sophistication, and large-scale empirical psychological testing. These studies showed no significant differences between males and females in overall intelligence and demonstrated that, while men were more likely to be at the very low end of the IQ scale, they were not equally likely to be at the high end.

Charles Darwin was among the most prominent adherents of the concept of greater male variability. In *The Descent of Man* ([1871] 1897), he argued that males are the engine of evolution, accumulating variations that lead to species divergence and evolution. For this reason, he wrote, "Man is more courageous, pugnacious, and energetic than woman, and has a more inventive genius" (557). In the nineteenth and early twentieth centuries, the principal evidence for the greater male variability hypothesis was the long-observed predominance of males among residents of what were then known as institutions for the "feeble-minded" and, conversely, among the ranks of genius and the socially eminent. Early twentieth-century observations of an excess of males among the intellectually disabled and documentation of a large number of mentally impairing X-linked conditions exclusive to males led to speculations that the single X was a mechanism for the observed "greater variability" in male intellect—and that the double X was a source of female dullness (Stevenson et al. 1994, 538).

[5] While it is certainly true that a second X shields females from many X-linked diseases, the presence of "extra" genetic material cannot be said to establish any of these claims to female superiority. After all, chimpanzees and corn have more DNA than humans.

The earliest geneticist to attach the X to male variability and female conservatism was Clarence E. McClung (1899, 1902), who first discovered the link between the X and sex. McClung later wrote of the X chromosome, "It is possible that we have here the explanation of the greater variability of the male" (1918, 162). He continued, "There is a possibility that in the male, the sex [X] chromosome being unmated, or opposed by an inactive element, may be more free to react with the other chromosomes and in this way change their constitution, being in turn affected by the reaction. By the nature of its transmission it must, after this experience, pass into the female line where its relation to the complex is necessarily different. The contrast in these two conditions is obvious and the interpretation strongly suggested" (162). The X-chromosomal theory of male intellectual superiority cyclically resurfaced in sex difference research throughout the twentieth century, and continues to lurk in X chromosome studies today. As the BBC reported in 2005: "Men also have another reason for feeling upbeat about their genetic lot. *New Scientist* reports that although men are more likely to be mentally retarded, they are also more likely to be geniuses. Although the average IQ of men and women is equal, men are more frequently found at both extremes of intelligence. This is because, if you have very good intelligence genes on your X chromosome, it pays not to have them muffled by more average genes on another X chromosome" (Kettlewell 2005). Robert Lehrke's *Sex Linkage of Intelligence* (1997) exhumes and reasserts, in near entirety, the greater male variability theory of the late nineteenth and early twentieth centuries. Ongoing research programs at the Medical Research Council in London and University of California–Los Angeles in the United States continue to engage in X chromosome research on the subject—a pursuit that has only been heightened in the wake of the sequencing of the human X in 2005. As a *Nature* article puts it, today "the 'feminine' X chromosome is a prime hunting ground for geneticists interested in the evolution of the cognitive and cultural sophistication that defines the human species" (Check 2005, 266).

Tracking the female X into human genetics

The cases of Turner and Klinefelter syndromes demonstrate how the idea of the female-engendering X was carried forward into the human genetics era and how the notion of the female chromosome continued to inflect reasoning about human health and biology even after the X was found not to determine femaleness in humans. Both Turner and Klinefelter were well-documented syndromes of gonadal dysgenesis prior to human chro-

mosome research. Physicians in the United States identified Turner syndrome in 1938 as a syndromic—meaning characterized by a complex of symptoms not localized to any single organ system—phenotype found exclusively in women. Traits included short stature, infertility, and neck webbing (Turner 1938). A Massachusetts General Hospital physician described Klinefelter syndrome in 1942 as a disorder of gonadal underdevelopment in males, resulting in hormonal deficiencies causing infertility and limited body hair (Klinefelter, Reifenstein, and Albright 1942).

Barr body screening in the 1950s revealed that Turner females lack a second X and that Klinefelter males carry an extra X. Once associated with sex chromosome aneuploidy in the 1950s, the disorders were redescribed in more strongly sexed and gendered terms. The infertility of the XO Turner woman was portrayed as evidence of her masculinity rather than a disorder of female sexual development and of development in general. Turner women were claimed to have masculine cognitive traits such as facility with spatiality, discomfort with female gender roles, and defeminized body shape. XXY Klinefelter males were portrayed as feminine, with much emphasis on their purportedly unmuscular body frame, female body-fat distribution, lack of body hair, and infertility. The eminent British geneticist Michael Polanyi even proposed that XO females were "sex-reversed males" (Harper 2006, 79). Patricia A. Jacobs and John Anderson Strong (1959) described an XXY individual as "an apparent male . . . with poor facial hair-growth and a high-pitched voice" (302). They continued, "There are strong grounds, both observational and genetic, for believing that human beings with chromatin-positive nuclei are *genetic females* having two X chromosomes. The possibility cannot be excluded, however, that the additional chromosome is an autosome carrying feminizing genes" (302). A 1967 *New York Times* article similarly captures this mode of reasoning. With the headline "If her chromosomes add up, a woman is sure to be woman," it describes XXY males as having "a few female traits" (Brody 1967, 28). Studies were even undertaken to determine whether Turner women show a tendency toward lesbianism or Klinefelter men incline toward homosexuality or cross-dressing.[6]

These assumptions about the X as feminizing distorted understanding of these disorders, stigmatized individuals carrying them, and misdirected research and clinical care. Today, clinicians specializing in Klinefelter and Turner management emphasize that these are not diseases of gender confusion. Klinefelter patients are phenotypic males, and Klinefelter is not a

[6] See also Miller (2006) on the deliberations over the true gender of Turner and Klinefelter individuals in the decade after the discovery of the Barr body.

syndrome of feminization. We now know that Klinefelter is one of the most common genetic abnormalities and often has so few manifestations that men live out their lives never knowing of their extra X. Writes Robert Bock (1993), "For this reason, the term 'Klinefelter syndrome' has fallen out of favor with medical researchers. Most prefer to describe men and boys having the extra chromosome as 'XXY males.'" Similarly, XOs are phenotypic females. Turner syndrome, which has more profound and systemic phenotypic effects than XXY, is emphatically not a masculinizing condition. Physical deformities, heart trouble, infertility, and, occasionally, social and cognitive difficulties are the principal concerns for Turner females.

Throughout the history of twentieth-century genetics, gendered conceptions of the X chromosome fueled ideological conceptions of femaleness and maleness. Today the conception of the X as the female chromosome is not obsolete. It remains a common assumption in twenty-first-century genomics and a source of distortion and bias in genetic reasoning. We have already visited, briefly, some of the areas in which the female chromosome appears in contemporary biomedical research: the surprise over the finding of spermatogenesis genes on the X chromosome and X-linked theories of sex differences in intelligence. Perhaps the most prominent case of how the sexing of the X as female continues to operate today, however, is found in "X mosaicism" theories of female biology, health, and behavior.

Female X mosaicism

Mammalian females are genetic mosaics for the X chromosome. In order to equalize the expression of X-linked gene products in males and females, one of the Xs in each somatic cell is randomly inactivated early in female development. Approximately half of a female's cells will express the maternal X chromosome and half the paternal X chromosome. Thus, females have two populations of cells, identical with respect to the twenty-two pairs of autosomes but variable in X-chromosomal gene expression when females carry functionally different versions of an X-chromosomal allele.

X mosaicism has some implications for human female biology. Random X inactivation early in development leaves most women with a 50 : 50 ratio of cells expressing either their paternal or maternal Xs. As a result, females carrying a disease allele on one of their X chromosomes will generally not develop the disease, since cells carrying the other X usually produce adequate amounts of the needed gene product to compensate for any dysfunction. For this reason, X mosaicism shields females from X-

linked diseases. Classic X-linked diseases such as Duchenne muscular dystrophy or hemophilia are infrequent in women and generally affect only men.

In rare cases, X mosaicism will begin to skew, resulting in tissues biased toward the maternal or paternal X chromosome. Tissues grow clonally, so skewing can happen randomly as a result of a bias in the cells from which the tissue grows. As we age, chromosomes fray, whither, and disappear due to the erosion of genetic repair mechanisms, making skewing more common. Usually, skewed X mosaicism has no phenotypic consequence and goes unnoticed. If a woman carries an X chromosome disease allele, however, extreme skewed X inactivation leading to dominance of the chromosome carrying the disease-causing allele can, in rare cases, cause women to exhibit classic X-linked diseases generally restricted to men. Thus, the primary clinical implication of skewed X mosaicism for females is that it may leave them functionally monosomic for the X—like males—making them vulnerable to male-typical X-linked diseases.

Developed in the 1960s by British cytogeneticist Mary Lyon, the X inactivation hypothesis began as a theory of an evolutionary fix that could equalize the X gene product between males and females (Lyon 1992). It was transformed in the 1980s and 1990s into a theory of genetic difference between males and females, and among females. Today, X chromosome mosaicism, the consequence of random X inactivation, is strongly identified with femaleness and used loosely and flexibly, often without any gesture toward experimental validation, to explain biological sex differences. The identification of the X with females, the cultural association of females with chimerism, and the assumption that the sex binary observed in the world will eventually be revealed at the molecular level help to fill in the gaps in the X mosaicism theory of sex differences, veil its empirical deficiencies, and glue its premises together.

Gender in X mosaicism research

From its inception, the hypothesis that females are cellular mosaics for X-chromosomal genes was received as confirmation of dominant cultural assumptions about gender difference. The characterization of females as mosaics or chimeras resonated with conceptions of women as more mysterious, contradictory, complicated, emotional, or changeable.[7] The future

[7] In biology, a genetic mosaic is distinct from a genetic chimera. Mosaics carry two different types of cells, whereas chimeras are made up of fused cells of two individuals or

Nobel laureate molecular biologist Joshua Lederberg wrote in 1966, "The chimerical nature of woman has been a preoccupation of poets since the dawn of literature. Recent medical research has given unexpected scientific weight to this concept of femininity" (1966, E7).[8] Reporting on the new finding in 1963, *Time* magazine asserted that "the cocktail-party bore who laces his chatter with the tiresome cliché about 'crazy, mixed-up women' has more medical science on his side than he knows. . . . Even normal women, it appears, are mixtures of two different types of cells, or what the researchers call 'genetic mosaics'" ("Research Makes It Official," 1963).

Today, the notion of X mosaicism as scientific confirmation of traditional ideological conceptions of female instability, contradiction, mystery, complexity, and emotionality is thoroughly entrenched. As science writer Nicholas Wade told the *New York Times* in 2005, "Women are mosaics, one could even say chimeras, in the sense that they are made up of two different kinds of cell. Whereas men are pure and uncomplicated, being made up of just a single kind of cell throughout" (Dowd 2005). A 2005 Pennsylvania State University press release similarly announced, "For every man who thinks women are complex, there's new evidence they're correct; at least when it comes to their genes" ("Men and Women," 2005).

These metaphors and gender assumptions are widely shared by present-day sex chromosome researchers. Duke University geneticist Huntington Willard, for instance, is quoted saying, "Genetically speaking, if you've met one man, you've met them all. We are, I hate to say it, predictable. You can't say that about women," and Massachusetts Institute of Technology geneticist David Page says, "Women's chromosomes have more complexity, which men view as unpredictability" (Dowd 2005). British geneticist Robin Lovell-Badge has similarly said that "10% [of genes on the X] are sometimes inactivated and sometimes not, giving a mechanism to make women much more genetically variable than men. I always thought they were more interesting!" (Kettlewell 2005).

Barbara Migeon, the Johns Hopkins X chromosome geneticist mentioned above and author of the book *Females Are Mosaics* (2007), is a leading promoter of the theory that X mosaicism is a fundamental mechanism of sex differences and a hallmark of female biology and behavior. Migeon claims that "somatic cellular mosaicism . . . has a profound in-

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species. "Mosaic" and "chimera" are used interchangeably and with the same connotations in the literature on X mosaicism, however, and I follow suit here.

[8] Lederberg also notes, however, that the case of XXY males "complicates the myth that chimerism is femininity" (1966, E7).

fluence on the phenotype of mammalian females" (1994, 230). According to Migeon, X mosaicism "creates biological differences between the sexes that affect every aspect of their lives, not just the sexual ones" (2007, 211). Migeon proposes that "cellular mosaicism . . . is likely to contribute to some of the gender differences in behavior" (209), including females' response to humor and differences in aggression, emotionality, and educational performance between males and females (2006, 1432–33). Molecular research on X chromosome mosaicism, Migeon argues, offers a promising platform for uncovering sex differences in the brain that studies of brain anatomy have not, thus far, revealed: "Despite dramatically different behavior between the sexes, surprisingly few anatomical differences have been identified," she writes, "[Perhaps] mosaicism for X-linked genes . . . may contribute to some of these sex differences in behavior" (2007, 211).

These speculative scientific conceptions of X mosaicism and femaleness are present in popular discourse around gender differences. Science reporter Natalie Angier, in *Woman: An Intimate Geography* (1999), celebrates female X chromosome mosaicism as a privilege of womanhood and a source of special womanly qualities. "Every daughter," she writes, "is a walking mosaic of clamorous and quiet chromosomes, of fatherly sermons and maternal advice, while every son has but his mother's voice to guide him" (25). She posits what she calls "the mystical X" as a source of "female intuition" and asserts that women "have . . . with the mosaicism of our chromosomes, a potential for considerable brain complexity" (25). Angier imagines a woman's X chromosomes as animating her brain with conflicting voices: "a woman's mind is truly a syncopated pulse of mother and father voices, each speaking through whichever X, maternal or paternal, happens to be active in a given brain cell" (25).

Female X mosaicism is also invoked to bring the authoritative veneer of molecular science to traditional and pejorative views of femininity. Bainbridge's *The X in Sex: How the X Chromosome Controls Our Lives* (2003), for instance, asserts that X chromosome mosaicism confirms that "women are mixed creatures and men are not . . . in a way far deeper" than previously thought (130). Citing the roots of this notion in the Christian vision of Mary as "both virgin and mother" (129), Bainbridge claims that women "represent some intermediate hybrid state" (128), revealed in their "unpredictable, capricious nature" (127). X mosaicism is a "natural reminder of just how deeply ingrained the mixed nature of women actually is" (148), writes Bainbridge. He continues: "So women's bodies truly are mixed—in a very real way. . . . Each woman is one creature and yet two intermingled" (151).

Case study: X mosaicism theories of female autoimmunity

The case of X mosaicism theories of female autoimmunity shows clearly how contemporary biomedicine continues to find resources in the mercurial links between the X chromosome and femaleness. Autoimmune disorders are more prevalent in women than men.[9] The current medical model holds that autoimmunity occurs when the immune system misrecognizes the body's own tissues as invaders, leading the system, finely tuned to eliminate foreign agents, to continually attack the body's tissues with all of its resources. Some researchers, noting the female prevalence of autoimmune diseases and seeing a parallel between the self-on-self attacks of autoimmunity and mosaic female tissues made up of cells expressing the maternal or paternal X chromosome, have sought a mechanism for autoimmunity in X mosaicism. These theories draw on the notion that the X chromosome mediates female biology and health, as well as gender-inscribed conceptions of the female body as fundamentally chimeric, to link female autoimmunity to X mosaicism.[10]

The most basic version of the X mosaicism hypothesis of female autoimmunity is that simple mosaicism of the X chromosome, in cases in which the X produces two conflicting immune products, leads to autoimmunity. There is also a more sophisticated version, which holds that if mosaicism is skewed so that an immunologically relevant organ, such as the thymus gland, contains a majority of one X, the immune system may misrecognize tissues that carry the other X, leading to an autoimmune reaction (Kast 1977; Stewart 1998). Evidence for X mosaicism hypotheses of female autoimmunity has been sought in studies of skewed X mosaicism in women with autoimmune disorders. In these studies, researchers look at the percentage of cells carrying the maternal or paternal X chromosome (typically in a blood sample). When one predominates, if it is above a threshold of either 80 or 90 percent, the woman is deemed to have skewed X mosaicism.

[9] For statistics on male and female incidence and prevalence of autoimmune diseases, see Jacobson et al. (1997), Walsh and Rau (2000), Lockshin (2006), Eaton et al. (2007), Cooper, Bynum, and Somers (2009), and McCombe, Greer, and Mackay (2009).

[10] Feminist science studies scholars Donna Haraway (1991), Emily Martin (1999), and Lisa H. Weasel (2001) are among those who have explored the relationship between immunity discourse and gendered metaphors and imagery, unpacking the parallels between "horror autotoxis" (medical researcher Paul Ehrlich's 1957 term for autoimmunity) and traditional conceptions of femininity. As Martin (1999) notes, the greater susceptibility of females to autoimmune disease, leading to suggestions that females are biologically "hybrid" (101) and "mixed-up" (103), aligns with ideological notions of females as double, divided against themselves, contradictory, unstable, and lacking in unitary selfhood.

These studies provide little evidence that X mosaicism is implicated in female predominance in autoimmunity. A higher rate of skewed X mosaicism than the general population has been demonstrated in just two cases: scleroderma (Ozbalkan et al. 2005) and autoimmune thyroid disorders (Ozcelik et al. 2006). It has not been found in the cases of lupus (Invernizzi et al. 2007), multiple sclerosis (Accelerated Cure Project 2006; Knudsen et al. 2007; Knudsen 2009), type 1 diabetes (Chitnis et al. 2000), or juvenile rheumatoid arthritis (Seldin et al. 1999), nor has it been found in the female-predominant and potentially autoimmune disorders of simple goiter (Brix et al. 2009) and recurrent pregnancy loss (Pasquier et al. 2007). There is conflicting, weak, or ambiguous evidence of an association with skewed X mosaicism in the case of primary biliary cirrhosis (Invernizzi 2007; Svyryd et al. 2010) and adult onset rheumatoid arthritis (Svyryd et al. 2010).

Even if studies were to document high rates of X skewing in women with certain autoimmune disorders, this would not, in any case, constitute sufficient evidence that skewed X mosaicism predisposes women to those disorders or that women are more inclined, in general, to autoimmunity. First, almost all X mosaicism studies use blood samples, looking at peripheral lymphocytes rather than cell types within the immune reaction pathways or organ systems of interest. This limits their significance. For example, women with the skin disease scleroderma show skewed mosaicism in their blood, but this skewing was not also found in the skin cells—the tissue of interest for the disorder in question. Second, these studies do not rigorously account for the confounding effect of age. Rates of both autoimmunity and X skewing increase with age in women (Russell et al. 2007), and to date studies of X mosaicism pattern variation do not persuasively disambiguate aging and autoimmunity.[11] Third, the X mosaicism hypothesis does not explain enough specific features of female predominance in autoimmunity to stand as a candidate for an explanation of the greater prevalence of autoimmunity in females. For example, the theory cannot explain the following: why the incidence of autoimmunity, but not the severity of the disease, differs between males and females; why female predominance is much more pronounced among the cohort di-

[11] The background picture of diversity of X mosaicism patterns in the general female population is also, on the whole, not well understood. James Amos-Landgraf et al. (2006), in the most credible study of its kind, looked at patterns in 1,005 phenotypically unaffected females, finding that skewing was relatively common. The study reported that fully 25 percent of females had patterns skewed at least to 70:30 and concluded that "with advancing age, there is greater variation in X inactivation-ratio distribution" (497).

agnosed with autoimmune disorders under age 40, with rates becoming more equal between the sexes as they age; why some autoimmune disorders are female predominant, some are male predominant, and others are sex neutral; how X mosaicism interacts with the significant and well-documented role of environmental factors involved in sex differences in autoimmunity (such as chemicals in cosmetics or the workplace); and finally, why there is wide variability in sex ratios of autoimmune diseases between different ethnicities, nations, and in developed versus less-developed regions of the world (see Lockshin 2006, 2010; Oliver and Silman 2009).

In sum, although research is ongoing, the evidence for the X mosaicism hypothesis of female autoimmunity is weak. Degree of X skewing has not been found to be a predictive biomarker of autoimmunity, nor of response to therapy, and it has not been demonstratively linked to autoimmunity in animal models or in humans. Yet researchers confidently assert that X mosaicism mediates female autoimmunity: "autoimmune diseases revolve around the sex chromosomes," writes Carlo Selmi (2008, 913). Zoltan Spolarics (2007) claims that "X-chromosome mosaicism represents an adaptive cellular system" (599) bestowing females with "potentially two distinct regulatory and response arsenals" (598) and predisposing them to autoimmunity.

Such assertions by biomedical researchers that the XX chromosome complement inclines women to autoimmunity are clearly unwarranted. Studies of associations between X mosaicism patterns and autoimmunity do not substantiate a causal link between the two phenomena, nor do they show precisely how the presence of two populations of cells might contribute to autoimmune reactions. The evidence suggests, rather, that X mosaicism is far from a general theory of, or a major factor in, higher rates of autoimmune disorders in females.

The notion that X mosaicism underlies female autoimmunity has become so commonplace that it now regularly appears as authoritative medical knowledge in health news reports and is considered a leading viable hypothesis in much of the literature on autoimmunity.[12] The immediate credibility given by molecular biologists to X mosaicism theories of female autoimmunity, and the theory's widespread uncritical repetition in a variety of research, clinical, and health media contexts, requires explanation given the theory's weak empirical basis. The credulous reception of the

[12] See, e.g., *Nature Genetics* (2000), Kruszelnicki (2004), Davies (2005), McCoy (2009), and Tingen (2009).

theory is driven in part by the stubborn and commonplace belief, documented in this essay, that the gender binary of male and female is present, writ molecular, in the sex chromosomes. Just as the Y is putatively the male chromosome, the X chromosome must, it is assumed, be a fundamental mediator of femaleness. Rooted in notions of the X as female, and chimerism as feminine, X mosaicism theories of female autoimmunity, I argue, present a contemporary case of synecdochic gendered conceptions of sex in biology leading to flawed scientific reasoning.

Conclusion

Currently, there is a broad popular, scientific, and medical conception of the X chromosome as the mediator of the differences between males and females, as the carrier of female-specific traits, or otherwise as a substrate of femaleness. As this essay has documented, associations between the X and femaleness are the accumulated product of contingent historical and material processes and events, and they are inflected by beliefs rooted in gender ideology. The still very contemporary view that the double X makes females unpredictable, mysterious, chimeric, and conservative, while the single X allows men to learn, evolve, and have bigger brains but also makes them the more risk taking of the two sexes, shows how conceptions of X chromosome structure and function often reflect and support traditional gender stereotypes.

In light of the empirical and conceptual weaknesses of these theories, scientists must work to develop alternative models of the relationship between the X and sex. They must cultivate an active practice of gender criticality, exposing their theories to rigorous examination from all perspectives. While the presence of a single X in males and a double X in females does have different implications for male and female biology, historical and contemporary speculations over the relation between the X and femaleness show that this assumption has consistently contributed to erroneous biological reasoning and that the X has been overburdened with explaining female biology and sex differences. As this essay has shown, the X chromosome has not only become female identified as an object of biological research, but has, more broadly, become a highly gendered screen upon which cultural theories of sex and gender difference have been projected throughout the twentieth century and up to the present day. The case of how the X became the female chromosome presents a prominent example of how unquestioned gender assumptions can distort

and mislead, not only within the biological sciences but more generally in the production of knowledge.

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